UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/910,087	07/20/2001	Peter Anthony Koopman	10981AZ	2931

7590 01/29/2003

Scully, Scott, Murphy & Presser
400 Garden City Plaza
Garden City, NY 11530

EXAMINER
NGUYEN, DAVE TRONG

ART UNIT	PAPER NUMBER
1632	6

DATE MAILED: 01/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/910,087	Koopman
Examiner	**Art Unit**
Dave Nguyen	1632

-- *The MAILING DATE of this communication appears on the cover sheet with the correspond nce address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be availeble under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 7, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *7-18* is/are pending in the application.

4a) Of the above, claim(s) *7, 9-13, 17, and 18* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *8 and 14-16* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Jul 20, 2001* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 1
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Applicant's election with traverse of the Group II claims, claims 8, 14-16, drawn to a gene therapy method of employing SEQ ID NO: 20, and homologous sequences having at least 79% in sequence identity, in Paper No. 5 is acknowledged. The traversal is that since the mouse Sox-9 gene (SEQ ID NO: 18) and the human sox-9 gene all belong to the Sox-9 family, the inventions I and II are not independent and distinct, particularly since the court in *In re Kuehl* states that applicants may describe in the manner required by 35 USC 112 all aspects as to what they regard as their invention, regardless of the number of statutory classes involved. The traversal is not persuasive because not only applicant attempts to claim a gene therapy method wherein distinct mouse Sox-9 gene is employed in Group I claims, applicant also attempt to claim an enormous number of therapeutic DNA having at least 79% to the mouse Sox-9 gene. As such, and regardless of whether the mouse and human Sox-9 genes belongs to the same Sox-9 family, the examiner maintains that the two and/or variants thereof are distinct molecules, and a search and examination for patentability of the mouse Sox-9 gene does not necessarily lead to the same consclusion for that of the human Sox-9 gene and variants thereof. Applicant also traverses that the classification system is defective and that the restriction is improper by relying on the classification system. The examiner maintains that the issue is whether or not protein therapy or gene therapy are independent and distinct from one another. In this particular instance, a search and examination of protein therapy for patentablity is clearly not the same as search and examination of gene therapy. Each requires distinct materials, method steps, let alone the distinct effect generated by recombinant proteins when administered *in vivo* vs. recombinant and/or exogenous DNA when administered *in vivo*. The art of gene therapy is not the same as the art of protein therapy and there is no evidence to disprove the distinction. As such, the classification system was just another supporting factor to further show the distinct inventions as stated in the restriction, and thus, the examiner maintains that the restriction is proper and made final. Applicant's traversal with respect to applicant's legitimate patent rights and applicant's financial burden is also not found persuasive because insofar as the

examiner has provided a sufficient reason for independent and distinct inventions, the restriction is still proper, and as such, an undue burden is clearly on the examiner to search and examine all of the groups. As a result of distinct issues and amount of prior art that the examiner has to conduct to search and examine completely all of the presently pending claims, an undue burden given the constrain of examining time will be on the examiner.

Claims 7, 9, 10-13, 17-18 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claimed invention.

Claims 8, 14-16 are pending for examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C.§ 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8 and 14-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

The application reviewed the state of the prior art regarding known SOX genes and their biological functions as transcription factors which play a biological role during a development process (pages 2-5). Regarding SEQ ID NO: 20 (referred by the application as Human SOX-9 gene), the application indicates that the SOX-9 protein HMG box domain at amino acids 104-192 shares 71% similarity with the SRY HMG box and the c-terminal third of the protein, and has a proline- and

glutamine-rich region, similar to activation domains present in some transcription factors. In addition, the specification indicates the human SOX-9 protein (SEQ ID NO: 21 encoded by SEQ ID NO: 20) share 79.3% identity and 82.4% with the chicken SOX-9 coding protein sequence (GeneBank Accession No. U12533). However, the specification and the prior art of record does not provide sufficient guidance and/or evidence to show a reasonable correlation between the primary structure of any of the disclosed SOX-9 polypeptide sequences and the full scope of the presently pending claims.

The specification does not enable a skilled artisan to determine without undue experimentation as to which of the DNA sequences having up to 21% variation from SEQ ID NO: 20 exhibits a biological function as a "SOX-9" protein. The application does not identify any and/or all of those amino acid residues/base pairs encoded by the nucleotide residues in SEQ ID NO: 20, which contain more than 2000 nucleotide residues, are essential for their biological activity and structural integrity. The specification does not teach which of the residues/bases from SEQ ID NO: 20 are expendable or substitutable. Further, no guidance to make any and/or all variants having 21% variation from either SEQ ID NO: 18 or 20, for example, is provided that would enable one skilled in the art to identity or produce all of the claimed sequences that retain the "SOX-9 type" activity, without undue experimentation, nor are there sufficient prior art teachings to enable one skilled in the art to identity or produce such a nucleic acid sequence, which precludes one from reasonably predicting the result of different modifications to the sequence without an undue experimentation. The state of the art as to the prediction of a biological activity of a polypeptide on the basis of its primary sequence including deletions and/or substitutions and/or additions remains unpredictable at the time the invention was made. The problem of predicting protein structure from mere sequence data of a single amino acid or nucleic acid sequence and in turn utilizing predicted structural determinations to ascertain functional aspects of any nucleic acid sequence and finally what changes can be tolerated with respect thereto is complex and do not invariably follow empirical rules. Unpredictability is keyed on the fact that simple analysis of primary,

secondary, tertiary, and quaternary structure of a polypeptide is not well correlated with the ability of the encoded DNA product to its functional activity because the relationship between the amino acid sequence of a polypeptide and its tertiary and/or quaternary structure is not well understood and is not invariably predictable; and, thus, it is not apparent how one skilled in the art arrives at a representative number of species of protein variants that fall within the intended scope of the claims and exhibit the recited biological activity, *e.g.* SOX-9 type activity, without undue experimentation, on the basis of applicant's disclosure (see Ngo *et al.*, in: The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz *et al.*, (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495). Thus, it is not apparent how one skilled in the art determines which of the isolated recombinant polypeptide sequences as set forth in the claimed invention (having between 21% and 93.5% variation), exhibit the disclosed biological activity as a SOX-9 gene product, without undue experimentation, on the basis of applicant's disclosure.

With respect to the biological activity of the human Sox-9 gene or its encoded protein product, the application teaches that SEQ ID NO: 20 plays an important role in development (page 5), and that experimental bone fracture induces expression of the SOX-9 polypeptide (SEQ ID NO: 19). However, neither the application nor the incorporated references demonstrate any therapeutic effect in any animal having a bone or cartilage disease. The application contemplates that SEQ ID NO: 20 acts as transcription factors to induce cartilage formation *in vivo.* A simple expression of a Sox-9 protein during embryogenesis or *in vivo* does not appear to be the same as a therapeutically relevant effect. Mundlos *et al.* (FASEB J., 11, 2, 125-132, 1997) teach that many transcription factors are involved in the intricate process of skeletal formation, growth, and homeostasis, and that these processes include patterning events during condensation and differentiation of mesenchymal cells to form cartilage precursor of the future bones, the replacement of cartilage by bones through endochondral ossification, the growth of lone bones through proliferation and differentiation of chondrocytes in growth plates, and bone formation differentiation of osteoblasts from mesenchymal cells in areas of intramembraneous ossification. In

addition, Wright *et al.* (Nature Genetics, Vol. 9, 15-20, 1995) teach that gain and loss-of function analyses in transgenic mice will be necessary to elucidate the roles of SOX-9 in sex determination as well as in neural and skeletal development (p. 20). In addition, neither the application nor the claims recite which subjects and which bone diseases or disorders are affected by the claimed treatments, the target sites, the effective dosage for accomplishing a therapeutic effect *in vivo,* the administration routes, and the stated effect of the claimed methods which are essential for the success of the claimed treatments.

In addition, neither the application nor the claims recite which subjects and which bone diseases or disorders are affected by the claimed treatments, the target sites, the effective dosage for accomplishing a therapeutic effect *in vivo,* the administration routes, and the stated effect of the claimed methods which are essential for the success of the claimed treatments. Thus, it is not apparent how one skilled in the art practices the claimed invention, without undue experimentation, on the basis of applicant's disclosure.

More specifically as to gene therapy methods as claimed for regeneration of bone and cartilage in all animals including humans, amphibians, reptiles, and fish, the application provides no *in vivo* and/or *in vitro* examples to demonstrate the biological activity of any DNA sequence as claimed for regeneration of bone or cartilage. Major considerations for any gene transfer or gene therapy protocol involve issues such as amount of DNA constructs to be administered, what amount is considered to be therapeutically effective for all of the claimed nucleic acid molecules, the route and time course of administration, the sites of administration, successful uptake of the claimed DNA at the target site, expression of the DNA at the target site in amounts of effecting the claimed methods (Verma *et al.,* Nature, Vol. 389, pp. 239-242, 1997). None of these considerations are adequately addressed in the specification to enable others to practice the invention without the exercise of undue experimentation. Verma *et al.* specifically teach that problems including the lack of efficient delivery systems, lack of sustained expression remain formidable

challenges (page 239, column 1). Gunzburg *et al.* (Molecular Medicine Today, pp. 410-417, 1995) state that "clearly, there are many problems to be overcome before gene therapy becomes a widely used treatment, and it will probably only ever complement rather than replace existing therapies" (p. 417). Gunzburg *et al.* also state that "the efficiency of gene delivery is perhaps the most limiting technical problem; this will require extensive modifications to existing vector systems or even the construction and development of new gene delivery systems (p. 416, column 2, last paragraph). Furthermore, an artisan, attempting to make and use the claimed therapeutic compositions, would first look to the specification for guidance as to therapeutic genes to insert into these vectors, however, insofar as the gene therapy method of employing any human Sox-9 gene in the claimed methods, the specification is not enabled for all of the claimed sequences other than SEQ ID NO: 20. Next the artisan would look to the art to provide guidance as to how to use therapeutic genes in the treatment of diseases, however, as demonstrated by the preceding reasons, the art recognizes that gene therapy remains unpredictable. Furthermore, neither the specification nor the incorporated references provide sufficient guidance as to the appropriate dosage for each bone/cartilage disease to be treated or routes of administration or other important parameters of therapy in regard he regeneration of bone or cartilage at any target site in all animals. The state of the targeted gene therapy art remains unpredictable even in 1999. Meng *et al.* (Gene Therapy of Cancer, Chapter I, pp. 3-20, 1999) teach that factors including specific genes used for a treatment, gene delivery vectors, routes of administration, and gene expression are all critical for the success of a gene therapy method (pages 4-6). For example, Meng *et al.* teach that "it is difficult to prepare sufficiently high titers of retroviruses for *in vivo* gene therapy", that "the most significant drawback to adenoviruses, however, is that they elicit a strong host immune response", and that "although it may seem intuitive that a heightened immune response may be good in cancer gene therapy, it is less desirable on a practical scale because the immune response helps to eliminate the vector and to decrease the expression of the transduced gene" (p. 4, column 2, last paragraph). Meng *et al.* further teach that "although animal

studies have suggested low toxicity and excellent efficacy, these investigations have been limited by the use of immuno-deficient mice" (p. 6, column 1).

With respect to administration routes, Meng *et al.* teach that delivery of virally expressed genes by intravascular or intracavitary injections also presents barriers to the delivery of the target genes (p. 6, column 1). For example, Meng *et al.* state:

> In intravascular administration, instillation into a peripheral vein dilutes the vehicle, so only a small portion may ultimately reach the tumor. Intravascular administration also elicits a powerful immune response. Tropism for organs such as the liver, for example by adenovirus, can be a disadvantage if delivery is intended elsewhere or may be advantageous if the liver is the target. Even with regional intravascular administration, the virus must traverse the endothelial wall and travel against pressures within an expanding tumor mass. In the case of intracavitary administration (i.e., intrapleural or intraperitoneal), the surface of the tumor mass is coated by virus, but intratumoral delivery within a solid mass represents an important barrier (page 6, column 1).

The specification fails to provide sufficient guidance and/or evidence to address all of the major issues as to the unpredictability of nature of the art, and of gene therapy at the time the invention was made. Thus, when weighing the guidance from the disclosure and all of the evidences as a whole, especially the unpredictability of the activities Sox-9 encoded DNA sequences in the treatment of regenerating bones or cartilage in any animal, the lack of reasonable correlation between simple existence of endogenous Sox-9 during embryogenesis and a therapeutic effect in a treatment of any bone or cartilage associate disorder in any animal, and the reasonable unpredictability of gene therapy and/or targeted gene therapy, it is apparent that one skilled in the art would not be able to practice the claimed invention, without undue experimentation, at the time the invention was made, particularly on the basis of applicant's disclosure and the doubts expressed in the art of record. Note that it is known in

the art that while some progress has been made toward human gene therapy, only a handful of clinical trials and very limited anecdotal results has been reported to date. Thus, the unpredictability of a particular art area alone provides reasonable doubt as to the accuracy of the broad statement made in support of enablement of a claim.

In view of the nature of the invention, the unpredictability of gene therapy, the lack of sufficient guidance and/or working examples, and all of the reasons set forth above, it is not apparent how one skilled in the art reasonably extrapolates from the guidance and /or the working examples of the application to any of the claimed treatment methods, without undue experimentation, on the basis of applicant's disclosure.

Note that the references cited in this office action other than the Ming reference were provided to applicants previously in parent cases. Thus, the references will be cited in the PTO-892 but will not be provided again.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Trong Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER